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Prescription of antipsychotic medication to patients at ultra high risk of developing psychosis

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Little is known about medication prescription in a naturalistic setting to patients at ultra high risk (UHR) of developing psychosis. Antipsychotic medication prescription to UHR patients is not recommended in clinical practice guidelines based on the current evidence. The aim of this study is to investigate medication prescription to UHR patients in the Netherlands.
The frequency of antipsychotic medication prescription to UHR patients ($n=72$) was compared with the frequency of antipsychotic medication prescription to patients who were diagnosed with a *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition psychotic disorder at first diagnostic evaluation ($n=90$). Within the UHR group, frequency of antipsychotic medication prescription at baseline was compared between UHR patients who did make the transition to psychosis ($n=18$) and UHR patients who did not ($n=54$). No significant differences were found in antipsychotic medication prescription to UHR patients and to patients who turned out to have a florid psychosis: 51% in the psychotic group and 58% in the UHR group used no medication. Thirty-four percent in the psychotic group and 21% in the UHR group used antipsychotic medication. There was also no difference in medication prescription between UHR patients who did and did not make the transition to psychosis. More research should be aimed at developing and implementing clinical practice guidelines for the treatment of UHR patients. *Int Clin Psychopharmacol* **24:223–228 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

In the past decennia, the ultra-high-risk (UHR) state for developing psychosis has been a focus of research. According to international clinical practice guidelines for early psychosis, being at UHR for psychosis means having psychotic symptoms that are not severe or persistent enough to meet criteria for a diagnosis as such, and/or having a first-degree relative with a family history of any psychotic disorder plus significant decline in functioning (International Early Psychosis Association writing group, 2005). In a naturalistic setting, UHR patients receive a wide range of treatments including antipsychotic medication and psychotherapeutic interventions.

The dopamine hypothesis of schizophrenia states that positive symptoms of psychosis, such as delusions and hallucinations, originate from an excess of dopamine in the mesolimbic system in the brain. With antipsychotic medication acting as a dopamine D_2 blocker, psychotic symptoms remit or decrease (Kahn and Davidson, 1993). However, treatment with antipsychotic medication often leads to side effects such as weight gain and sedation. As UHR patients are not yet psychotic, by prescribing antipsychotic medication to UHR patients the disadvantages outweigh the advantages. In most studies, the transition percentage to a psychosis in UHR patients is 20–40% (McGlashan *et al.*, 2003). Therefore, UHR patients will be exposed to side effects, but not necessarily to the benefits of antipsychotic medication prescription because of the chance of being a 'false positive'. False positives are patients identified as being at UHR for psychosis who will never make the transition to psychosis.

When antipsychotic medication is prescribed to UHR patients, it is usually done in low doses. Recent studies suggest, however, that long-term use of antipsychotic medication, even in low doses can cause sensitization of dopamine receptors in the brain and that a psychosis, also called supersensitivity psychosis or rapid-onset psychosis, could follow cessation of this antipsychotic medication (Moncrieff, 2006). Therefore, the question arises as to how long should antipsychotics be prescribed to the UHR patient after starting treatment with antipsychotic medication. These issues are addressed in the clinical practice guidelines for early psychosis (International Early Psychosis Association Writing Group, 2005), but research is necessary to investigate whether these guidelines are followed in clinical practice.

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In this naturalistic study, medication prescription to UHR patients in the Netherlands was examined. We investigated whether there was a difference in the frequency of antipsychotic medication prescription to patients who were referred for a second opinion with a suspected UHR status but who turned out to have a florid psychosis (i.e. a score of 6 on one or more of the positive items of the Structured Interview for Prodromal Syndromes for more than a week) and patients with UHR symptoms. We hypothesized that antipsychotic medication was more often prescribed to patients with florid psychosis than to UHR patients at first diagnostic evaluation at our department. In addition, we expected that UHR patients who did make the transition to psychosis were prescribed antipsychotic medication more often than UHR patients who did not make the transition to psychosis, because symptoms may be more severe in the group that does make a transition to psychosis.

Methods

Participants

Participants were selected through our clinical research program in early psychosis at the Academic Medical Center, Amsterdam, The Netherlands. Most patients were referred for a second opinion by practitioners in secondary mental healthcare institutions who suspected a psychotic development. Diagnostic evaluation was performed in 251 patients, of which 72 patients (28.7%) had UHR symptoms and were included in the study and 90 patients (35.9%) were diagnosed with a florid *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) psychotic disorder. These patients were also included in this study. Other patients did not meet the criteria for UHR symptoms or had another disorder and were therefore not included. The included UHR patients were followed up in a naturalistic study with the major focus on the course of UHR symptomatology.

The inclusion criteria for the UHR group were: age between 12 and 35 years, being able and willing to give informed consent and belonging to one or more of the following four groups: (i) familial risk plus reduced functioning: individuals with a DSM-IV schizotypal personality disorder or a first-degree relative with a history of any DSM-IV psychotic disorder and a change in mental state or functioning in the patient leading to a reduction of 30% or more on the Global Assessment of Functioning (GAF) Scale. A 'best estimate' derived from an independent interview with the patient and a close relative, mostly one of the parents, defines the initial baseline of functioning. (ii) Attenuated psychotic symptoms: presence of at least one of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, odd thinking and speech, paranoid ideation. These symptoms should occur at least several times a week and should have been present for at least 1 week. (iii) Brief, limited, or intermittent psychotic symptoms: a history of psychotic symptoms, such as hallucinations, delusions, and odd behavior or appearance, with a duration of less than 1 week and spontaneous remission. (iv) Basic symptoms: presence of at least two basic symptoms. Basic symptoms are self-perceived disturbances in cognition, perception, and social interaction, which have been found to be predictive of a psychotic episode.

The exclusion criteria for the UHR group were: previous psychotic episode for more than 1 week [as assessed with the Structured Clinical Interview for Diagnosis, sections B and C (Spitzer *et al.*, 1992)], caused by substance abuse [as assessed with the Comprehensive International Diagnostic Interview, sections J and L (World Health Organization, 1993)], caused by an organic mental disorder, IQ below 85 [as assessed with the Dutch National Adult Reading Test (Schmand *et al.*, 1991)].

For the psychotic group, the inclusion criteria were: age between 12 and 35 years and meeting DSM-IV criteria for a psychotic disorder. Forty-five out of 90 patients met DSM-IV criteria (American Psychiatric Association, 1994) for the diagnosis of schizophrenia (50%), 15 patients met criteria for schizophreniform disorder (16.6%), 18 patients met criteria for psychosis not otherwise specified (20%), 11 patients for schizoaffective disorder (12.2%), and one for delusional disorder (1.1%). The exclusion criteria were the same as for the UHR group, except for having had a previous psychotic episode for more than 1 week.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethics Committee of the Academic Medical Center. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Instruments

The prepsychotic symptoms were assessed with the following two questionnaires: the Structured Interview for Prodromal Syndromes (SIPS) is a semistructured interview in which UHR symptoms in the past 3 months are assessed (Miller *et al.*, 2003). The SIPS is a comprehensive diagnostic tool designed specifically for the assessment of the whole spectrum of prodromal signs and symptoms. The scale is composed of 19 items (five positive, six negative, four disorganization, four general symptoms) each of which is given a score of 0–6 according to defined criteria. A score between 3 and 5 on the positive symptoms indicates attenuated psychotic symptoms and a score of 6 indicates a psychotic state. These symptoms should occur at least several times a week and should have been present for at least 1 week.

The Bonn Scale for the Assessment of Basic Symptoms-Prediction scale (BSABS-P) was developed to assess 'basic symptoms' (Klosterkötter *et al.*, 2001). The BSABS-P is a semistructured interview that consists of 33 principal items and can be divided into five BSABS-subscales: cognitive thought disorders, additional symptoms with positive predictive value, visual perception disorders, acoustic perception disorders, and cognitive motor disorders. The symptoms are rated on a scale starting from 0 (not present/absent) to 6 (severe).

Global functioning was measured by the Global Assessment of Functioning (GAF) score. The GAF score is a score between 0 and 100 that indicates the overall psychological, social, and occupational functioning (American Psychiatric Association, 1994).

Medication prescription at first diagnostic evaluation was measured by dividing medication into four categories: (i) antipsychotic medication: patients using antipsychotic medication and antidepressants, and/or other medication, such as benzodiazepines, were also assigned to this category, (ii) antidepressants or antidepressants with medication other than antipsychotic medication, (iii) other, for instance, benzodiazepines, methylphenidate, and/or lithium carbonate, and (iv) no medication. Furthermore, analyses were performed with the two categories 'no medication' and 'medication' (category one, two, and three combined).

Procedure

After their referral, putative UHR patients were invited for a first interview with a psychiatrist and a psychologist. In this face-to-face diagnostic interview, which lasted for approximately 2 h, patients were asked about their lifetime history of complaints, family history of psychiatric disorders, drug and medicine use. Subsequently, in a standardized order, the SIPS and BSABS-P were conducted.

Simultaneously, in another interview, the parents or guardians were asked about the lifetime development of their child. All information needed was taken from the intake reports of the Amsterdam UHR study. Information obtained from the referrer about medication prescription was checked with the patient and parents. Further relevant information from these intake reports was entered into a database.

Ratings were given based on the SOPS and BSABS-P and a staff meeting was held to discuss all the available information about the patient. When considered at 'UHR', patients were asked to sign a written informed consent before participating in the project. In this naturalistic longitudinal cohort study, UHR patients were followed up for 3 years. They were referred back to their referring mental health institution. Some received treatment; others were only monitored. Patients, their parents or caretakers, and the referring instances were asked to contact our department in case of increasing symptoms. In addition, a SIPS interview was conducted with the patients at 9, 18, and 24 months and they were again interviewed over telephone at 36 months. Patients who were diagnosed with a psychotic disorder at first diagnostic evaluation were referred to our clinical unit or elsewhere for treatment and were not followed up.

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 15.0.1; SPSS Inc., Chicago, Illinois, USA). Independent sample *t*-tests and χ^2 tests were used to compare means of demographic details. A χ^2 test was also used to compare medication use between groups. The dose of antipsychotic medication in chlorpromazine equivalents was compared between the psychotic and UHR group with an independent sample *t*-test and between the transition and no transition group with a nonparametric Mann–Whitney *U* test (because of small sample size). With a Cox regression analysis, we investigated prediction of psychosis in the UHR group, with medication status at baseline as the independent variable.

Results

Participants

Demographic details were compared for the psychotic group and the UHR group. Furthermore, the GAF score at intake was compared between the groups. The results are shown in Table 1.

Only GAF score at intake showed a significant difference. The GAF score was lower for the psychotic group than for the UHR group ($t = 6.68$, d.f. = 160, $P = 0.0001$). Furthermore, demographic details were compared for the UHR group when divided into two groups: UHR patients who made the transition to psychosis and UHR patients who did not make the transition to psychosis. Table 2 shows the results of the two groups.

Table 1 Demographic details of the psychotic and ultra-high-risk groups

	Psychotic at intake ($n=90$)	Ultra high risk ($n=72$)
Sex		
Male	71	47
Female	19	25
Age at intake		
Mean	20.31	19.40
SD	4.19	3.88
GAF score		
Mean	39.44	50.18*
SD	10.53	9.59

GAF, Global Assessment of Functioning.
*$P=0.0001$.

The mean interval between inclusion and transition of this group was 12.77 months (range = 3.00–35.00, SD = 7.86). After transition to psychosis, patients received the following diagnoses: schizophrenia ($n = 12$), schizophreniform disorder ($n = 3$), schizoaffective disorder ($n = 2$), and brief psychotic disorder ($n = 1$). Eight patients (11%) were lost to follow-up. The patients with follow-up information did not differ significantly from those who were lost to follow-up in terms of sex, age, severity of positive and negative symptoms, basic symptoms, global functioning, and family predisposition.

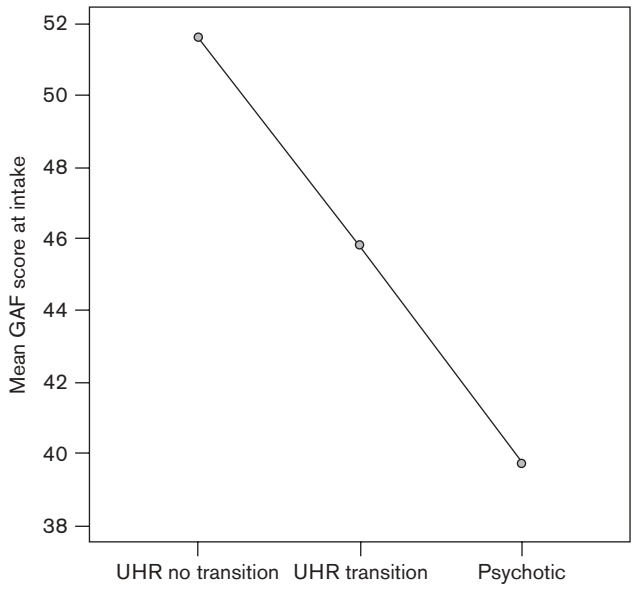
Only the GAF score at intake showed a significant difference between groups. The GAF score was significantly lower for the transition group than for the no transition group ($t = 2.26$, d.f. = 70, $P = 0.03$). The GAF scores are shown in Fig. 1.

Table 2 Demographic details of the ultra-high-risk group at baseline, divided into the transition and no transition groups

	Transition ($n=18$)	No transition ($n=54$)
Sex		
Male	13	34
Female	5	20
Age at intake		
Mean	20.17	19.15
SD	4.09	3.81
GAF score		
Mean	45.83	51.63*
SD	8.11	9.73

GAF, Global Assessment of Functioning.
*$P=0.027$.

Fig. 1



Global Assessment of Functioning (GAF) score at intake. UHR, ultra high risk.

The psychotic group versus the ultra-high-risk group

Frequency of medication prescription within the psychotic group and the UHR group are presented in Table 3. Comparisons were made between medication prescription to the psychotic group and to the UHR group. There was no difference in the prescription of medication ($\chi^2 = 0.74$, d.f. = 1, $P = 0.4$). Furthermore, no difference was found when the prescription of medication was divided into the four categories ($\chi^2 = 5.40$, d.f. = 3, $P = 0.2$).

However, dose of antipsychotic medication in chlorpromazine equivalents was significantly different between the UHR group and the psychotic group. The psychotic group was prescribed a significantly higher dose than the UHR group (200.6 ± 131.0 vs. 78.1 ± 75.7; $t = -3.7$, $P < 0.001$).

The ultra-high-risk group divided into the transition group and the no transition group

Frequency of medication prescription within the UHR group that made the transition to psychosis and the UHR group that did not make the transition to psychosis are presented in Table 4.

Comparisons were made between medication prescription to the transition group and medication prescription to the no transition group. No difference was found in the prescription of medication ($\chi^2 = 0.69$, d.f. = 1, $P = 0.4$). No difference was found when the prescription of medication was divided into the four categories either ($\chi^2 = 2.51$, d.f. = 3, $P = 0.5$). Three cells had an expected count of less than 5. Medication prescription in two and four categories was not predictive for a future psychotic decompensation (Wald = 0.28, $P = 0.6$, relative risk = 0.8 and Wald = 0, $P = 0.99$, relative risk = 1).

Table 3 Medication prescription in the psychotic group and the ultra-high-risk group (number of patients)

	Psychotic group		Ultra-high-risk group	
	Frequency	Percentage	Frequency	Percentage
No medication	46	51.1	42	58.3
Antipsychotics	31	34.4	15	20.8
Antidepressants	9	10.0	7	9.7
Other	4	4.4	8	11.1
Total	90	100.0	72	100.0

Table 4 Medication prescription in the transition group and no transition group (number of patients)

	Transition		No transition	
	Frequency	Percentage	Frequency	Percentage
No medication	9	50.0	33	61.1
Antipsychotics	6	33.3	9	16.7
Antidepressants	1	5.6	6	11.1
Other	2	11.1	6	11.1
Total	18	100.0	54	100.0

The dose of antipsychotic medication in chlorpromazine equivalents was also not significantly different between the UHR transition group and the UHR no transition group (60.7 ± 31.8 vs. 102.5 ± 114.0); $t = -0.25$, $P = 0.8$).

Discussion

The main result of this study of patients referred because of suspected UHR symptoms is that, contrary to expectations, there is no difference in medication prescription between patients with UHR symptoms and patients already suffering from florid psychosis at first diagnostic evaluation. However, psychotic patients were prescribed a significantly higher dose of antipsychotic medication than the UHR group. Furthermore, contrary to expectations, no significant difference was found in the frequency of medication prescription between UHR patients who make the transition to psychosis and UHR patients who do not make the transition to psychosis. We did find a significant difference in the GAF score between the psychotic and the UHR group, and between the transition and no transition group. As it was not clear at intake who among the UHR patients would later make the transition to psychosis, the significantly lower GAF score at intake of the transition group compared with the no transition group is interesting. This result suggests that the GAF score is also useful in determining which of the patients may have an increased risk for developing a first psychotic episode. Other studies show the same results (Yung *et al.*, 2003, 2004b). We reported in another paper on the features that best predict transition to psychosis in our UHR group (Velthorst *et al.*, 2009).

The dose of antipsychotic medication in chlorpromazine equivalents was significantly different at baseline between the psychotic and the UHR group but not between the UHR transition and the no transition group. The patients diagnosed with a psychotic disorder at first diagnostic evaluation received a higher dose of antipsychotic medication than the UHR patients. Thus, 34% of the patients who were referred with a suspicion of UHR status and turned out to be psychotic did not yet receive the diagnosis of a psychotic disorder by the referrer but were already prescribed antipsychotic medication.

Antipsychotic medication and ultra-high-risk symptoms

The North American Prodrome Longitudinal Study also investigated the prescription of antipsychotic medication to patients with UHR symptoms during follow-up (Cannon *et al.*, 2008). Of the included UHR patients, 35.1% were prescribed antipsychotic medication during the follow-up interval. Cannon *et al.* (2008) reported that antipsychotic medication prescription was associated with an increased risk of conversion to psychosis. When controlled for symptom severity, however, this effect disappeared. The authors argue that this result was because of the possibility that the patients who received antipsychotic medication had more severe symptoms. In this study, more than one-third of prepsychotic, putatively prodromal patients do receive antipsychotics despite clinical practice guidelines (Yung *et al.*, 2004b; International Early Psychosis Association writing group, 2005) and the current evidence base. Thus, it is crucial for prodromal researchers to protocolize treatment algorithms, demand adherence to these, and carefully measure the treatment provided (McGorry *et al.*, 2008).

The Personal Assistance and Crisis Evaluation study carried out a clinical trial to examine the effect of a low-dose antipsychotic medication and cognitive behavioral therapy in UHR patients. The results showed that this treatment reduced the risk of making the transition to psychosis. A disadvantage of this study is, however, that the relative effect of the antipsychotic medication and the cognitive behavioral therapy could not be disentangled (McGorry *et al.*, 2002). The North American Prevention through Risk Identification, Management and Education study carried out a clinical trial to investigate the effect of antipsychotic medication (olanzapine) compared with a placebo in UHR patients (McGlashan *et al.*, 2003; Miller *et al.*, 2003). The results of this study showed that olanzapine did delay, but did not prevent the transition to psychosis (McGlashan *et al.*, 2006). Thus, although the use of antipsychotic medication by UHR patients does seem to have a positive effect on the short-term use in one study, the scientific evidence for the preventive effect of antipsychotic medication on UHR symptoms is scarce.

Thus, scientific evidence for the prescription of antipsychotic medication to UHR patients is flawed and the risks are substantial. The international guidelines (International Early Psychosis Association writing group, 2005) do not prevent prescribing antipsychotics to UHR patients in clinical practice. Research should be aimed at developing more elaborate and better validated guidelines and their implementation.

In this study, eight patients were lost to follow-up. Therefore, we are uncertain about their current state of functioning. A transition to psychosis is highly unlikely, because we asked the practitioner who referred the patients to contact us when they suspected a psychosis.

Early detection of psychosis

In our study, 46% of the patients who were floridly psychotic failed to receive antipsychotic medication. Psychosis is often not recognised in time by general practitioners or even in the mental health services (Larsen *et al.*, 1998; Johannessen *et al.*, 2005). Several other studies have found a large percentage of patients with a psychotic disorder in a sample referred with a suspicion of a psychotic development (Broome *et al.*, 2005; Nelson and Yung, 2007). An important function of

UHR projects could be earlier recognition of psychosis and therefore reduction of the duration of untreated psychosis.

Limitations

A limitation of the study is sample size, especially in the analyses of differences in the frequency of medication use between the UHR group with a transition to psychosis and the UHR group without a transition. In addition, wherever medication use was divided into four categories, the sample sizes were small. Our results should be replicated in a larger sample. Furthermore, we did not report on the duration of treatment with antipsychotic medication. Patients in the UHR group may have been prescribed antipsychotic medication for a shorter period of time than patients in the psychosis group.

Adequacy of *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition

In light of our results, it may be confusing for clinicians using the present DSM to decide whether patients should receive a diagnosis of psychotic disorder or not. For example, according to DSM-IV criteria, a patient can receive the diagnosis of brief psychotic disorder if they experience psychotic symptoms for at least a day. Subsuming UHR research of the past decennium, a patient experiencing psychotic symptoms for a day should receive UHR status and should not be treated with antipsychotic medication. To avoid antipsychotic medication prescription to UHR patients, duration of psychotic symptoms should be at least a week. If DSM-IV has a more dimensional structure, it would be helpful if psychosis would be defined on a dimension of not present to psychotic. The separation line between UHR and psychosis could be defined by frequency and duration criteria of psychotic symptoms as specified in the Comprehensive Assessment of At Risk Mental States (Yung *et al.*, 2004a, 2004b).

Implications

With respect to the treatment of UHR symptoms, cognitive therapy has been suggested. A randomized controlled trial compared cognitive therapy with monitoring in UHR patients (Morrison *et al.*, 2004). The results showed that cognitive therapy significantly reduced the likelihood of a transition to psychosis and of being prescribed antipsychotic medication. A cognitive therapy multicenter trial has been started in 2008 in four Dutch cities: The Hague, Amsterdam, Leiden, and Leeuwarden. Future research may help in quick and adequate recognition and treatment of psychosis and the development and implementation of treatment protocols for UHR patients.

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